0022-202X/79/7305-0368$02.00/0
THE JOURNAL OF INVESTIGATIVE DERMATOLOGY, 73:368–372, 1979

Vol. 73, No. 5, Part I
Printed in U.S.A.

# Concurrent Linear Scleroderma and Systemic Lupus Erythematosus: A Report of Two Cases

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**Two patients with linear scleroderma (*en coup de sabre*) developed systemic lupus erythematosus (SLE). This association has been well documented in only one previous case. The presence of high titer antibodies to ribonucleoprotein (RNP) initially led to the diagnosis of the mixed connective tissue disease. Development of more serious clinical involvement and antibodies to Sm (case 1) or native deoxyribonucleic acid (nDNA) (case 2) helped establish a diagnosis of SLE. Use of these studies in the differential diagnosis of systemic rheumatic diseases is discussed briefly. The presence of anti-RNP antibodies in patients with localized scleroderma may herald a more serious rheumatic disease.**

We wish to report 2 unusual patients with coexistent linear scleroderma and SLE who presented with high titers of antibody to the RNP component of extractable nuclear antigen (ENA). ENA is a crude saline extract of thymus comprised of a number of antigens including the ribonuclease (RNase) and trypsin-sensitive nuclear antigen known as RNP and the RNase-resistant, trypsin-resistant Sm antigen [1–3]. These antigens can be detected by hemagglutination reactions or gel diffusion [1,3,4]. A syndrome in which high titer serum antibody to RNP and clinical features of more than one connective tissue disease, including systemic sclerosis, SLE, rheumatoid arthritis, and polymyositis are present is known as the mixed connective tissue disease (MCTD) [5]. Patients with this syndrome appear to exhibit a more benign course and may have a reduced incidence of serious renal involvement [1,3,5-10]. Since the ARA preliminary criteria for SLE were satisfied in our 2 patients, we believe they represent examples of 2 concomitant diseases, linear scleroderma and SLE, despite the fact they also fit the clinical spectrum of MCTD [11].

The use of the term "MCTD" may delay recognition of a more serious disease in patients with high titers of antibody to nuclear RNP. It is essential to observe these patients carefully and to test them periodically for appearance of other antinuclear antibodies that may indicate development of a more serious disease process.

## *Investigational Studies*

Antinuclear antibodies (ANA) were detected by standard immunofluorescence methods using mouse liver sections [12]. Antibodies to nDNA were detected by precipitation with ammonium sulfate (Farr technique) [13]. Antibodies to Sm and RNP were measured by double immunodiffusion (Ouchterlony) as previously described [4]. Briefly, antigen was extracted from young rabbit thymus (Pel Freeze Biologicals, Rogers, Arkansas), as reported by Kurata and Tan [14]. RNP activity was destroyed by prior incubation of antigens with pancreatic RNase (Type III-A, Sigma Chemical Co., St. Louis, Missouri). Sm and RNP were identified by the presence of identity arcs with reference serums to these antigens, and the absence of a reaction with RNase-treated antigen confirmed the presence of RNP.

Skin biopsy specimens were immediately frozen in liquid nitrogen and stored at −70°C until sectioned. Direct immunofluorescence (IF) staining was performed by methods previously described, using monospecific fluorescein-conjugated antisera to IgG, IgM, IgA, C3, C1q and fibrin [15].

Sera for immune complex studies were separated from freshly drawn blood and kept frozen at −70°C until tested. Each sample was assayed by 2 different methods for the detection of circulating immune complexes: (1) The monoclonal rheumatoid factor (mRF) inhibition assay performed by the method of Luthra et al [16], and (2) the C1q binding assay performed by the method of Nydegger et al [17], with modifications described by Tappeiner et al [18].

## *Case 1*

A 23-yr-old Mexican-American woman was referred to the Dermatology Clinic in July 1977 with a rash on her face and upper arms which had recurred every summer for 6 yr. She also complained of the recent onset of arthralgias and fatigue, but denied fever, weight loss, dysphagia, or Raynaud's phenomenon. Her only medication was a topical steroid cream. She was first seen by a dermatologist for hair loss 3 years prior to this visit. At that time, a linear scarring lesion of the scalp was noted which showed changes consistent with morphea histologically. One year later a facial lesion was biopsied which revealed changes characteristic of lupus erythematosus. At that time, an ANA was positive at 1:80, and a diagnosis of discoid lupus erythematosus was made.

When evaluated, abnormalities were limited to the skin. Discoid, slightly erythematous papules and hyperpigmented macules were noted on her cheeks and upper arms. A 10 cm linear scalp lesion with alopecia and depressed sclerosis, but

Manuscript received March 5, 1979; accepted for publication June 5, 1979.

This work was supported by in part by Grant AI 14550 from the National Institutes of Health and by the Medical Research Service of the Veterans Administration.

Dr. Mackel is a recipient of the United States Public Health Service Fellowship Award, No. 1 F32 AM0637-01.

Dr. Kozin is a recipient of a Clinical Investigator Award from the National Institute of Arthritis, Metabolism and Digestive Diseases, 5K08-AM 00483-01.

Dr. Jordon is a recipient of a Medical Career Investigatorship of the Veterans Administration.

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Abbreviations:
ANA: antinuclear antibodies
ARA: American Rheumatism Association
ENA: extractable nuclear antigen
IF: immunofluorescence
MCTD: mixed connective tissue disease
mRF: monoclonal rheumatoid factor
nDNA: native deoxyribonucleic acid
RNase: ribonuclease
RNP: ribonucleoprotein
SLE: systemic lupus erythematosus

without erythematous borders, was present. A total leukocyte count was 3800/mm$^3$ with a normal differential, and an erythrocyte sedimentation rate (Westergren) was 56 mm/hr. The following tests were normal or negative: hemoglobin, VDRL, serum immunoglobulins, cryoglobulins, BUN, creatinine, SGOT, bilirubin, lactic acid dehydrogenase, alkaline phosphatase, uric acid, glucose, CPK, calcium, phosphorus, serum electrolytes and creatinine clearance. Chest X-ray, EKG and barium swallow were normal. A urinalysis revealed 60–100 WBCs and bacteria, but no protein or erythrocytes; the culture grew >100,000 colonies of *Escherichia coli*. Serologic tests were as follows: LE cell preparation, positive; ANA, positive at 1:480 in a homogeneous pattern; rheumatoid factor, positive at 1:160; $CH_{50}$, 68 mg/dl (normal 89–132 mg/dl); $C_4$, 9 mg/dl (normal 12–72 mg/dl); anti-nDNA antibodies, 15.6% (normal <11%); and ENA, positive for both anti-RNP antibody at a serum dilution of 1:4 and anti-Sm antibody, neat (Fig 1).

Histologically, the scalp lesion demonstrated diffuse fibrosis and hyalinization of dermal collagen with entrapment of the sweat glands, a pattern consistent with scleroderma (Fig 2). By direct IF, biopsies of normal exposed forearm skin and normal nonexposed buttock skin showed dermal-epidermal deposition of IgG, IgM, C3, C1q and fibrin in a granular pattern. Deposition of IgM, C3 and fibrin in superficial blood vessels was noted. Epidermal nuclear staining was not observed. Low levels of immune complexes were detected by both C1q binding and mRF inhibition assays.

A presumptive diagnosis of SLE and concurrent linear scleroderma was made, since the patient fulfilled the preliminary ARA criteria for SLE (discoid LE skin lesions, alopecia, leukopenia, and positive LE cells/ANA) [11]. She was treated with hydroxychloroquin (200 mg/day) and sunscreens. Her urinary tract infection was treated with an antibiotic.

The patient's rash gradually cleared, the arthralgias diminished, but the scalp lesion remained unchanged. The rheumatoid factor, $CH_{50}$, and CBC returned to normal, and the ESR decreased to 28 mm/hr. Anti-nDNA antibody titers remained normal. In January 1978, the ANA was 1:1000 with a speckled pattern. In July 1978, repeat direct IF of normal exposed forearm skin showed minimal IgM deposition at the dermal-epidermal junction.

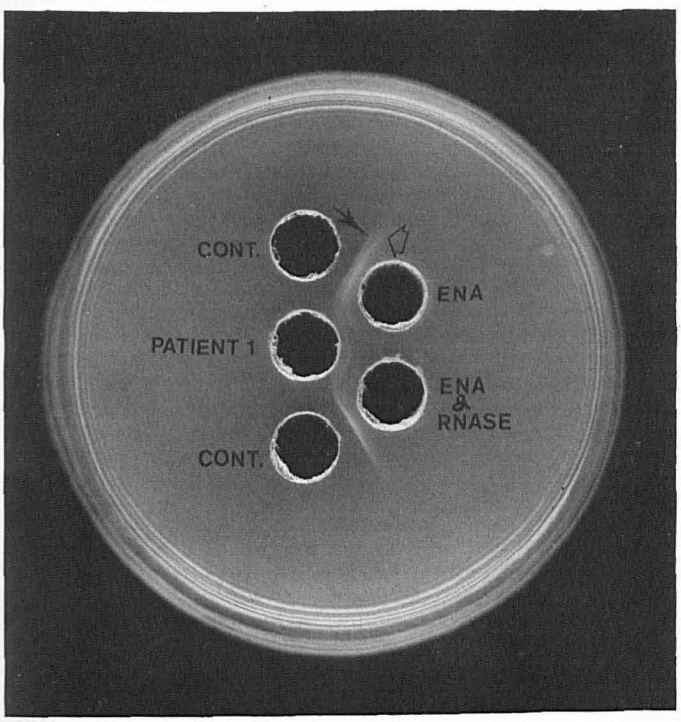


FIG 1. *Case 1.* Double diffusion of serum and control known to contain antibodies to both Sm (*closed arrow*) and RNP (*open arrow*). Note lines of identity between this case and control serum and disappearance of the anti-RNP-RNP line after treatment of antigen with RNase.

FIG 2. *Case1.* Biopsy specimen of scalp lesion showing epidermal atrophy and diffuse fibrosis of dermis (hematoxylin-eosin, reduced from ×50).

*Case 2*

In July 1975, a 9-yr-old native American girl was admitted to Milwaukee Children's Hospital with a 2-day history of fever, fatigue, and arthritis of the hands, knees and ankles. Her past medical history was unremarkable except for a lesion of the forehead which had been present for approximately 1 yr. A biopsy of this lesion demonstrated thickening of dermal collagen with atrophy of rete pegs; these changes are characteristic of scleroderma.

On physical examination, a depressed, depigmented sclerotic lesion extended along the midline from her nose to the hairline. Malar erythema was apparent. Fusiform swelling of the fingers and warmth and swelling of the knees and feet were present.

Laboratory studies showed a normal CBC, BUN, creatinine, alkaline phosphatase, bilirubin and urinalysis. Other studies were as follows: LDH, 1050 IU (normal 40-110 IU); SGOT, 156 IU (normal 5–30 IU); aldolase, 1.532 IU (normal 0.285–0612 IU); and ESR, 65 mm/hr (Westergren). Serum protein electrophoresis revealed a polyclonal gammopathy. Additional studies included a positive LE cell preparation, positive ANA with a speckled pattern, a negative rheumatoid factor, and negative anti-nDNA antibodies (performed elsewhere). Anti-RNP antibodies were found at a titer of 1:10,000 (hemagglutination method, also performed elsewhere). Chest X-ray, esophagram

and IVP were normal. A diagnosis of MCTD was made, and treatment with aspirin was initiated.

The patient was well until November 1975 when she was rehospitalized because of fatigue and severe diarrhea. In addition to the malar erythema and the *en coup de sabre* lesion, a violacious hue was noted around her eyes. Purpuric lesions were present on both legs and around her waist. In addition to the previous serological abnormalities, a depressed C3 of 64 mg/dl (normal 116–164 mg/dl) was found. The urinalysis showed 1+ protein, 3+ hemoglobin and numerous red blood cells. Skin biopsy of an erythematous macule on her leg showed no evidence of leukocytoclastic vasculitis. A kidney biopsy was attempted but was unsuccessful. A muscle biopsy showed changes consistent with polymyositis. The patient was treated with 10 mg prednisone daily.

In July 1976, a successful renal biopsy was performed and showed membranoproliferative glomerulonephritis and IF staining with anti-IgG, IgA, IgM and C3. Despite treatment with high doses of prednisone, her renal function deteriorated. The renal biopsy was repeated in August 1977 and showed interstitial nephritis as well as membranoproliferative glomerulonephritis. Cyclophosphamide was started but discontinued after 11 days due to leukopenia.

In July 1978, she returned to the hospital with nausea, vomiting, diarrhea and oliguria. Her blood pressure was 170/110, BUN 196 mg/dl and serum creatinine 16 mg/dl. She was transferred to the Milwaukee County Medical Complex for hemodialysis. In addition to renal failure, she had pleural and pericardial effusions and a Coombs-positive hemolytic anemia. Direct IF of normal skin showed blood vessel deposition of IgM and epidermal nuclear speckling with IgG. No dermal-epidermal fluorescence was apparent (Fig 3). Anti-RNP antibodies were detected at a serum dilution of 1:512, but no anti-Sm antibody was apparent (Fig 4). The ANA was positive at 1:5120, speckled, and anti-nDNA antibody was elevated with 82% binding. Serum, obtained in 1977 and stored at −70°C, was tested for immune complexes by the C1q and mRF radioassays. High levels of circulating immune complexes were detected by the C1q binding assay, while the mRF radioassay was normal. Similar values were obtained from serum prior to dialysis in 1978, but postdialysis levels were normal.

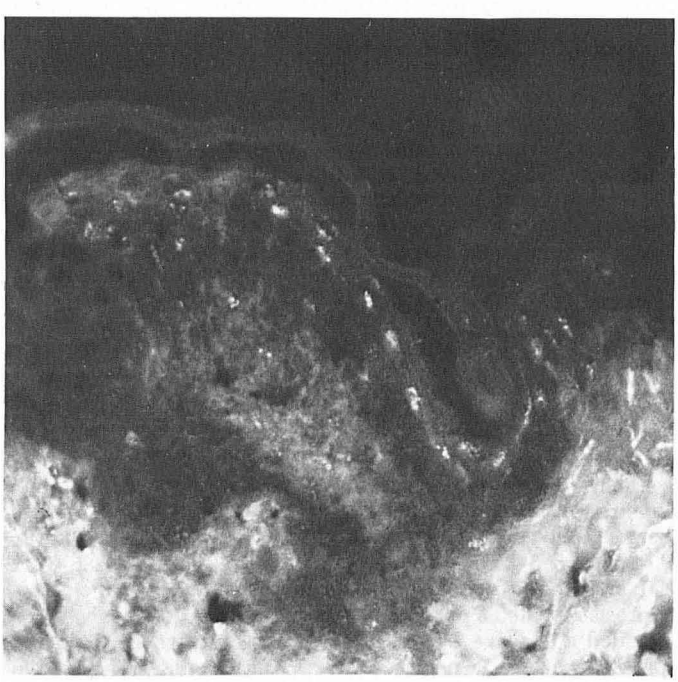

FIG 3. *Case 2.* Direct immunofluorescence of normal skin showing epidermal nuclear speckling with anti-IgG (reduced from ×250).

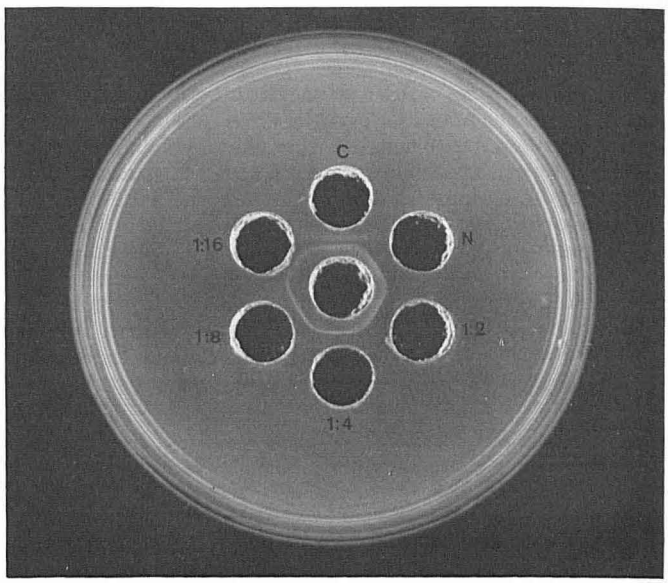


FIG 4. *Case 2.* Double diffusion of serum versus untreated ENA. Note the presence of both anti-Sm and anti-RNP antibodies in control (*C*) well. Anti-RNP is present in titers of 1:16 in this illustration.

## DISCUSSION

The 2 patients described here had coexistent linear scleroderma and SLE. In both cases, the linear scleroderma developed several years before the onset of SLE. The association of these 2 diseases has been well documented in only one previously reported case [19,20] although it has been suggested by several authors (Table) [21,22].

Overlap syndromes in which features of several connective tissue diseases are present are well recognized [23–27]. As many as 12% of patients with progressive systemic sclerosis (scleroderma) also have clinical features of SLE [20]. However, this does not appear to be true for patients with the more benign or localized forms of scleroderma, linear scleroderma and morphea, since our review of the literature has disclosed only 1 definite and 4 possible cases (Table).

Another overlap syndrome recently described by Sharp and co-workers is the MCTD [5]. Clinically, the MCTD syndrome is characterized by features of scleroderma (Raynaud's phenomenon, dysphagia, hand and finger edema, and sclerodactaly), SLE (skin changes and photosensitivity, and neurologic, renal and hematologic abnormalities), polymyositis and rheumatoid arthritis [5,7,9,10]. It has been suggested that the MCTD is a more benign disease than SLE, since renal involvement is less common and less severe when present [1,3,5–10]. Patients with MCTD have high titers of circulating antibody to a saline extractable antigen from crude thymus preparations which are sensitive to RNase digestion [1–3]. This antigen, RNP, is not specific for the MCTD as it is found in 15–25% of patients with SLE, 9–22% of patients with scleroderma, and in a number of other rheumatic diseases [28–30]. While antibody to RNP has been detected in at least 1 other patient with localized scleroderma [3], the true frequency of this antibody in linear scleroderma or morphea is not known.

The presence of other antinuclear antibodies may be useful in differentiating these systemic connective tissue diseases. Antibody to Sm, an acidic nuclear antigen, is thought to be highly specific for SLE [30]. This antigen is also obtained by saline extraction of thymus, but antibodies to Sm can be differentiated from RNP by their resistance to RNase and the presence of identity arcs in agarose gels when standard reference sera are used [4]. Antibodies to nDNA are virtually pathognomonic of SLE, while anti-single stranded DNA antibodies may be found in other connective tissue diseases [30]. A

*A review of cases with coexistent linear scleroderma or morphea and SLE*

| Reference | Cutaneous diagnosis | Duration until diagnosis of SLE (yr) | Clinical features of SLE | Laboratory findings | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Direct IF | LE Cells | ANA | Anti-nDNA | Anti-RNP | Anti-Sm |
| Tufanelli et al<br>Dubois et al<br>(Case 12)[a] | LS | 12 | Facial erythema, photosensitivity<br>Arthritis<br>Leukopenia<br>Renal disease (proteinuria) | 0 | + | 0 | − | 0 | 0 |
| Dubois et al | | | | | | | | | |
| Case 13 | M | 11 | Discoid LE, photosensitivity<br>Malar rash<br>Arthritis | 0 | + | 0 | − | 0 | 0 |
| Case 14[b] | M | ? | Arthralgia | 0 | + | 0 | − | 0 | 0 |
| Scarola, Shulman | LS | 15 | Not described | 0 | 0 | 0 | 0 | 0 | 0 |
| Umbert, Winkelman | LS | 3 | Discoid LE, leukopenia | + | ± | 0 | ± | 0 | 0 |
| Mackel et al[c] | | | | | | | | | |
| Case 1 | LS | 3 | Arthirtis, leukopenia<br>Discoid LE, alopecia (±) | + | + | + | − | + | + |
| Case 2 | LS | 1 | Arthritis, polyserositis<br>Malar rash, hemolytic anemia<br>Glomerulonephritis | − | + | + | + | + | − |

[a] This was the same patient reported initially by Tuffanelli (personal communication).
[b] This patient does not fulfill ARA preliminary criteria for SLE.
[c] Present report: LS = linear scleroderma; M = morphea; + = present; − = absent; and 0 = not reported.

number of other antinuclear antibodies have been identified and their clinical associations defined; this subject has recently been reviewed [32,33].

It is of interest that both patients reported here had antibodies to RNP and initially were thought to have the MCTD syndrome. Some of the clinical and laboratory findings in our patients, including arthritis, presence of positive lupus band test, depressed total hemolytic complement, leukopenia and histopathologic features of SLE or scleroderma, have been seen in patients with MCTD [5–7,34,35]. However, the presence of anti-Sm antibodies in case 1 and anti-nDNA antibodies in case 2 are indicative of SLE.

Using the term "MCTD" may be helpful to the clinician when caring for patients who exhibit high levels of anti-RNP *alone* and a spectrum of clinical features which are not typical for any single connective tissue disease, since these patients appear to have a better prognosis than those with SLE [1,3,5–10]. But, as case 2 demonstrates, it is important to observe these patients carefully for the development of clinical or serologic signs which would establish a more specific diagnosis. For example, when first examined, case 2 did not fulfill ARA criteria for the diagnosis of SLE [11], and a diagnosis of MCTD appeared to be more appropriate. Later, however, despite initial improvement with systemic steroids, she developed severe clinical and serological (anti-nDNA antibody) manifestations of SLE.

Another feature which has been noted in SLE and MCTD is epidermal nuclear speckling on direct IF of skin biopsy specimens [36,37] in the presence of high titer antibody to ENA. In case 2, epidermal nuclear staining was present, thus supporting these previous reports. However, this case emphasizes the fact that epidermal nuclear staining should not be interpreted as a diagnostic marker for a more benign connective tissue disease process, but only for the presence of high titer antibody to RNP. The onset of glomerulonephritis in case 2 reemphasizes the well-established prognostic importance of antibodies to nDNA [6,8,37,38].

The 2 patients presented here indicate that linear scleroderma in children may, in some cases, precede the development of SLE. It is possible that the presence of antibody to nuclear RNP in such patients may indicate their potential to develop SLE or systemic involvement. To determine the significance of these findings, it is important that the study of patients with linear scleroderma include a thorough and periodic immunological evluation.

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